

THE PHYSIOLOGY OF GROWTH

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Although clinical and experimental evidence had previously indicated that skeletal growth depended upon the pituitary gland, it was not until 1921 that Evans and Long, at the University of California, demonstrated that a saline emulsion made from the anterior pituitary lobe of fresh glands of cattle contained a growth hormone. The hypophyses were thrown into 40 per cent. ethyl alcohol, agitated with a glass rod, transferred to two changes of sterile normal saline, and triturated with force and speed with ocean sand, diluted with saline, and decanted. The layers of sand, cell fragments and opaque pink fluid permitted the latter to be decanted. This emulsion, when injected daily in doses of $\frac{1}{2}$ to 1 ml. intraperitoneally into young rats, accelerated their skeletal growth rate, compared with controls, and continued this growth for 200 days, or more, after growth normally ceases. Later, improved chemical methods permitted the preparations of alkaline extracts which contained the growth hormone in purer form. It is interesting and important to note that Evans (1923-4) recorded that success, in mammals, with parenteral injections of beef hypophysis extracts was only obtained 'after failure in a long series of massive oral administrations'. There is no doubt that in mammals the growth hormone is ineffective when given by mouth, although this well-established experimental fact is still ignored by some clinicians. The rat is a particularly suitable animal for testing growth hormone because its epiphyses remain open until late in life.

The effect of extracts containing pituitary growth hormone has also been dramatically demonstrated in hypophysectomized rats and in congenitally dwarfed mice. Evans (1923) termed his normal rats injected with pituitary emulsions 'hypophysis giants', and stated that they were 'twice as heavy as the largest individuals known to us from our own and published records for this animal species'. They were fat animals; 'the skeleton, most of the viscera especially the heart and lungs, liver, kidneys, and alimentary tract showed a true overgrowth, but not so the reproductive tract, the uterus and oviduct remaining infantile'. He also observed that the growth and maturation of ova were impaired or prevented, and

postulated an antagonism between growth and sex-stimulating hormones. Further observations suggested that corpora lutea were formed before ovulation occurred, and that his emulsions contained gonadotrophic luteinizing hormone. Although Evans' original giant rats were apparently adipose, later work (Lee and Schaffer, 1934), showed that there was a retention of nitrogen and a relative excess of body protein. This was also true of the excess of tissue deposited in and around the abdomen. Evans stated in a recent discussion in London that rats treated with pure growth hormone, unlike those in the initial experiments with crude extracts, were not adipose.

Another fundamental step was the development by P. E. Smith (1926) of a technique of complete hypophysectomy on the rat, without interfering with the hypothalamus. There resulted 'an almost complete growth stasis and a rapid regression in the size of the adrenals (involving chiefly the cortex), the thyroid and the sex apparatus' (Fig. 1). At the Institute of Biology at Berkeley University, California, rats are completely hypophysectomized without complications in about two minutes for each operation, and there is always a plentiful supply of hypophysectomized rats for experimental work. Such rats may be used for the assay of growth hormone, either by weight increase, or by tail growth (Freud *et al.*, 1935, 1939). Smith and MacDowell (1930) studied a strain of black silver dwarf mice, brought from England by Professor L. C. Dunn in 1928, in whom the characteristic of dwarfism was shown by Snell to be recessive. These mice cease to grow after the end of the second week, but, although there is some delay in sexual development, reproduction takes place. The essential physiological defect is absence of the growth hormone, and the essential histological defect in the pituitary gland of these animals is a complete absence of the eosinophil cells. Implantation of the pituitary glands of these dwarf mice into immature female mice of a normal strain produces no acceleration of growth but accelerates sexual development. The injection of growth hormone will produce growth in these dwarf mice. Further experimental evidence to the effect that the

eosinophil cells are the source of the growth hormone was provided by Smith who showed that the peripheral part of the bovine gland contains eosinophil cells, and, when stripped from the central basophil portion, will yield growth hormone. Clinically, gigantism is often associated with an eosinophil adenoma.

It is also of interest to note that the thyroid and adrenal cortex of Dunn's dwarf mice were hypoplastic, suggesting that the eosinophil cells are the source of the thyrotrophic and adreno-cortico-trophic hormones.

Measurement and Site of Action of Growth Hormone

Since the epiphyses of normal rats remain open in adult life, earlier methods of assay of growth hormone depended upon observations on the body weight of normal rats after 'a plateau' in their weight curve was established, indicating cessation of growth. After the technique of hypophysectomy was mastered, the effect on the weight of the hypophysectomized rat appeared to have a greater exactitude and specificity. Freud, Levie and Kroon (1939) used the tail of the hypophysectomized rat as a more exact measurement of the effect of the growth hormone (Fig. 2). They also made radiographic and histological studies of fundamental importance. Using an almost purified growth hormone, they demonstrated its specific chondrotrophic effect. In the normal growing rat, the epiphyseal zone shows cells arranged in columns, little cartilaginous matrix, vascular connective tissue and a fine network of cancellous bone. In the hypophysectomized rat (Fig. 1), the regular columns of cartilage cells characteristic of growing cartilage are undeveloped and irregularly placed, the longitudinal arrangement is lost, mitosis is minimal, the matrix has increased and the fine primary cancellous bone has disappeared. Growth hormone immediately repairs this histological picture, which reverts to normal, and shows active growth of cartilage. There is no alteration in the development of bone tissue itself, and the growth hormone is seen to have a biologically typical point of attack at the proliferating cartilage. Freud, Levie and Kroon (1934) found that the epiphyses of the tail of the rat soon become closed after hypophysectomy. Thus after four weeks a transverse bony plate closes the epiphysis, from which a number of massive bony processes project towards the diaphyseal marrow cavity. This can be entirely prevented by the early use of growth hormone after hypophysectomy, but it cannot be reversed after it has occurred. Smith (1930), however, found replacement therapy renewed growth three months after hypophysectomy.

Is there a Specific Growth Hormone ?

Pituitary extracts containing growth hormones were found by earlier observers to contain also adrenotrophic and thyrotrophic hormones as well as prolactin. Apart from any direct effect on skeletal growth attributable to hormones of the adrenal cortex and thyroid and possibly to prolactin, it is probable that these hormones have effects on metabolism which indirectly favour growth, especially in hypophysectomized animals in which these glands are hypoplastic or atrophic. Riddle and Bates (1938) suggested therefore that certain pituitary extracts owe their action upon growth to a balanced combination of prolactin, thyrotrophic and adrenotrophic hormones rather than to a special growth hormone. Earlier experiments, however, indicated that the growth hormone was a specific entity. Thus Evans (1924) records that Smith and Allen showed that beef hypophysis is effective by mouth in producing growth in hypophysectomized tadpoles, but that it does not produce metamorphosis or repair the atrophied adrenal cortex (interrenal body) or the thyroid. Smith, in 1930, demonstrated that whereas intramuscular transplantation of living pituitary glands from adult rats into dwarfed hypophysectomized rats restored the size and function of the thyroid, adrenals and gonads as well as producing growth, injections of a saline suspension of fresh gland affected growth only. It would therefore appear that although extracts of growth hormone as usually prepared contain adrenotrophic and thyrotrophic hormones which have some effect on growth, there is a specific growth hormone which can be chemically separated. This is in keeping with the existence of clinical conditions in which the only defect appears to be that of growth hormone, although other clinical conditions confirm that the thyroid, the adrenals and the gonads themselves have an important influence on growth. We shall see later that further purification of the growth hormone led to more conclusive proof of its specificity.

The Thyroid and Growth

In the strain of congenitally dwarfed mice referred to above, thyroid extract alone produced an increase of growth, although not as much as pituitary growth hormone (Bates *et al.*, 1935). The rate of growth of young normal mice is consistently accelerated by thyroxine injected daily, but the period of this acceleration lasts for only five weeks after which time the control mice overtake the treated animals and the ultimate size is the same. The skeleton of rats thyroidectomized at birth does not develop beyond the skeletal age of 15 days, even with pituitary growth extract, unless thyroid is also given (Salmon, 1941). Neverthe-

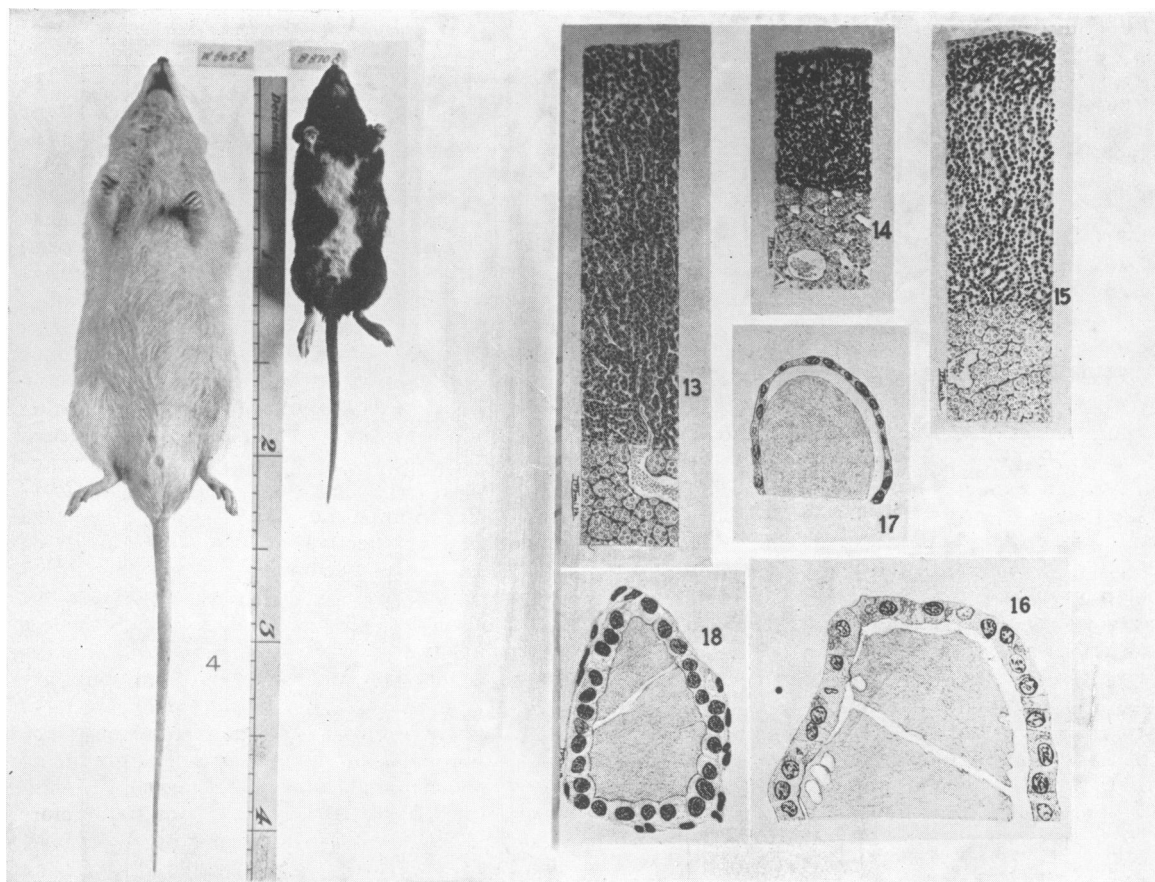


FIG. 1.—*Left:* Hypophysectomized rats (with litter-mate control) showing failure of growth after hypophysectomy at 26 days of age. (Photograph at 122 days.) *Right:* Nos. 13, 14 and 15 illustrate sections of adrenal cortex, normal rat, hypophysectomized rat and hypophysectomized rat given pituitary transplant. Nos. 16, 17 and 18 illustrate respectively sections of thyroid vesicles of normal rat, hypophysectomized rat and hypophysectomized rat given anterior pituitary transplant.

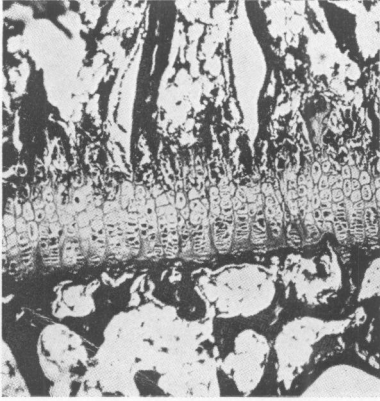
(By courtesy of Dr. P. E. Smith)

less, if the rats are thyroidectomized at 35 days of age, pituitary growth hormone will produce growth above that of normal rats, even without additional thyroid, although thyroid augments the effect. In thyroidectomized-hypophysectomized rats greatest growth is produced by pituitary growth hormone plus thyroid; considerable growth by pituitary growth hormone alone; but thyroid alone has no effect in the absence of the pituitary gland according to Evans, Simpson, and Pencharz (1939). Since thyroidectomy results in loss of the eosinophil cells from the pituitary gland, the resulting stunting of growth would appear to be due to the diminished or absent secretion of growth hormone, as well as to the diminished rate of metabolism.

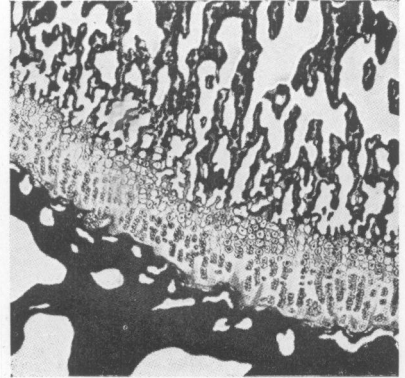
Sex Hormones and Growth

In some mammals such as dogs, testosterone or

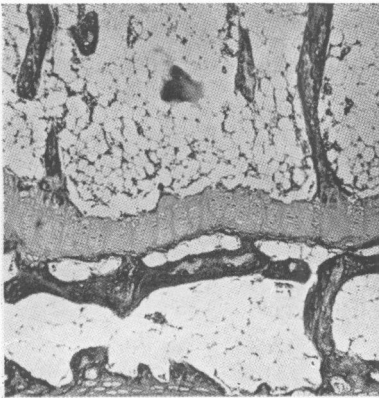
oestradiol produce dwarfing by inducing premature union of the epiphyses. Larger doses inhibit the secretion of growth hormone and cause degranulization of the chromophil cells of the pituitary. In mice, both testosterone and oestradiol cause an acceleration of certain age changes in the epiphyseal cartilage by inhibiting proliferation of the cartilage cells and by promoting degeneration and hyalinization of the cartilage and sclerosis and calcification of the cartilaginous growth substance (Silberberg and Silberberg, 1941). In 1939 Gaarenstroom and Levie showed that oestrone and diethyl stilboestrol inhibited tail-growth in rats. The epiphyseal apertures narrowed, the cartilage cells became smaller and decreased in number, the normal arrangements of cartilage cells in vertical columns became disordered and cartilage cells were resorbed. However, there was no closure of the epiphyseal junction by formation



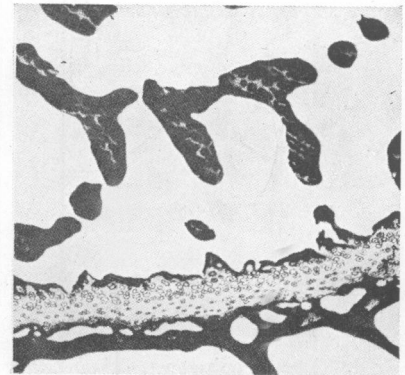
Tail vertebra, normal, Mallory. $\times 56$.



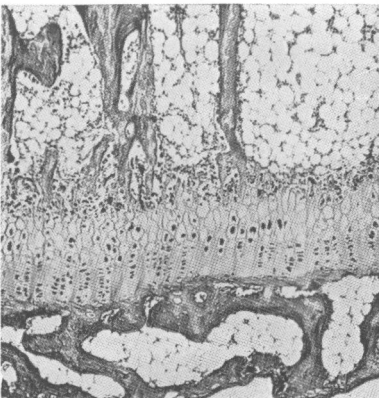
Schematic drawing of the tibia, normal, Mallory. $\times 56$.



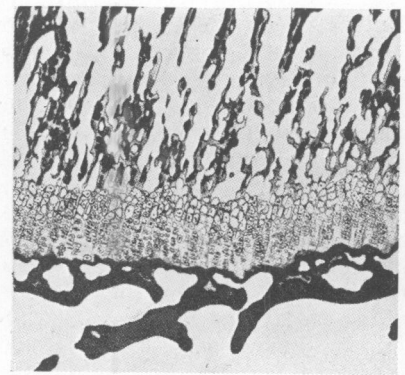
Tail vertebra, Hypophysectomized, Mallory. $\times 56$.



Schematic drawing of the tibia, Hypophysectomized, Mallory. $\times 56$.



Tail vertebra, Hypophysectomized and treated, Mallory. $\times 56$.



Schematic drawing of the tibia, Hypophysectomized and treated, Mallory. $\times 56$.

(By courtesy of J. Freud, L. H. Levie, and D. B. Kroon)

FIG. 2

of a transverse bony plate, as occurs after hypophysectomy. It was postulated that oestrone does not act merely by inhibiting pituitary growth hormone secretion, but by a direct action on the epiphyseal junction antagonistic to that of growth hormone. Reiss, Fernandez and Golla (1946) found, using the hypophysectomized rat, that testosterone (or oestrone) given at the same time as growth hormone, considerably diminished the normal action of the latter in producing growth of the tail, and that testosterone by itself could produce no growth of the tail at all in such hypophysectomized animals. Although their experiments indicate peripheral growth inhibiting action of sex hormones, the histological sections of the combined action of growth hormone and testosterone do not show serious disturbance of the structure of the epiphyseal cartilage or failure of repair after hypophysectomy. It is difficult to correlate the absence of growth augmenting effects of testosterone, or even more so its peripheral inhibitory effect, with the positive results in clinical medicine, e.g. in eunuchoidism and infantilism. Gardner and Pfeiffer (1943) found that oestrogens cause a deposition of calcium in the bones of mice, and refer to earlier observations that the blood calcium may rise considerably in birds during the maturation of the eggs with injected oestrogens. Simpson, Kibreck, Becks and Evans (1942), using young adult female rats, found that oestrogens caused an involution of the proximal growth cartilage, and although after three weeks' treatment the epiphyseal cartilage partially recovered its growth capacity, a striking mass of thick bony trabeculae filled the upper part of the diaphyseal marrow cavity.

Insulin and Growth

Growth is normally accompanied by nitrogen retention, and Mirsky (1939) suggested that the nitrogen-retaining action of anterior pituitary extracts is mediated, in part, by the islets of Langerhans of the pancreas. Young (1944, 1945), stated that the growth hormone has not been separated from the pituitary diabetogenic hormone. He further observed that in rats, where the pituitary 'diabetogenic' extract produces hypertrophy of the islets of Langerhans but not diabetes, growth is accompanied by nitrogen and water retention, and by a catabolism of fat. This is true in paired feeding experiments, and also where the injected rats are permitted to indulge an increased appetite, but in the latter experiments the loss of fat is not so great. In both types of experiments the rats appeared much fatter and better nourished than the uninjected controls. Analysis of the tissues, however, showed 18 per cent. protein, 7 per cent. fat and 60 per cent. water in the

injected rats, compared with 16 per cent. protein, 15 per cent. fat and 60 per cent. water in the control rats. Since the specific gravity of fat is less than unity while that of protein-containing tissue, with a substantial percentage of water, is above one, the injection of pituitary extract in Young's experiments led to a rise in specific gravity of the body mass and of its tissues. Young quotes the work of Lee and Schaffer (1934), referred to above, as showing a similar nitrogen retention effect of pituitary growth hormone.

Puppies were found by Young to behave as rats, but in older dogs increase in weight and growth usually stopped when diabetes developed. Even so a positive nitrogen balance was often sustained in the presence of glycosuria and ketonuria and with a maximum D/N ratio. When the animal became resistant to the pituitary diabetogenic extracts, the positive nitrogen balance reverted to normal at the same time as the glycosuria stopped. Young therefore concluded that the growth activity as indicated by this nitrogen retention, is closely related to the diabetogenic activity of a pituitary extract, and that the mechanism of 'growth hormone activity' consists of the induction of hyperfunction of the pancreatic islets and hypersecretion of insulin. If a closer correlation with epiphyseal cartilage growth is demonstrable, especially if the histological chondrotrophic effect of growth hormone can be induced by insulin action directly, the theory put forward will prove even more attractive. Further evidence for the insulotrophic and diabetogenic effects of purified growth hormone can be found in the work of Marx, Herring and Evans (1944), Gaarenstroom, Huble and de Jongh (1948), Cotes, Reid and Young (1949), and Campbell, Davidson, Snair and Lei (1950). An associated piece of evidence is the demonstration of a galactopoietic activity of purified anterior pituitary growth hormone by Cotes, Crichton, Folley and Young (1949), since such activity is found with the diabetogenic hormone. It seems justified, in the present state of knowledge, to conclude that the pancreatic islets can be considered as capable of playing a very important part in both experimentally induced or natural growth. This is not going so far as to conclude unequivocally that the growth hormone is identical with the pituitary pancreatotrophic (insulotrophic) hormone or the 'diabetogenic hormone.'

The Adrenals and Growth

The fact that early crude preparations of growth hormone contained adrenotrophic hormones gave rise to the suggestion that the adrenals played a part in growth. A preparation of pure growth hormone free from adrenotrophic hor-

none, and the preparation of pure adrenotropic hormone free from growth hormone, have negatived any direct augmenting effect on epiphyseal cartilage growth by the adrenals. Further, in Herbert Evans' laboratory (personal communication) pure growth hormone has produced giant rats after the animals have been adrenalectomized but maintained alive on salt. The normal physiological functions of the adrenals or some of these functions may, however, by their effect on metabolism ensure that normal endogenous growth hormone can exercise its optimum effects. Adrenalectomy may possibly influence the structure and function of the anterior pituitary gland in relation to the secretion of growth hormone, although the loss of chromophil cells after adrenalectomy appears to affect the basophil rather than the eosinophil cells.

In 1943, Evans, Simpson and Li drew attention to the inhibiting effect of adrenocorticotrophic hormone on the growth of male rats, an effect originally noted by Moon (1937). The inhibition did not occur in adrenalectomized rats. In a supplementary histological study with Becks and Marx (1944), they showed that A.C.T.H. alone hardly affected the tibial epiphyseal cartilage of hypophysectomized rats, but A.C.T.H. given with growth hormone reduced the reparative effect of growth hormone on this cartilage. In 1949, Li, Simpson and Evans found, in hypophysectomized rats fed on a limited quantity of food, that pure growth hormone caused an increase in protein and water content of the tissues of the carcass with a lowering of the fat content, whereas adrenocorticotrophic hormone resulted in a decrease in the water and a gain in the fat content. The protein content was unchanged, but in normal animals A.C.T.H. causes a reduction in the total weight of the animal, a loss of nitrogen from the tissues into the urine, and an increase of tissue fat (Li, 1950). Green (1950) demonstrated the inhibition of skin mitosis in the mouse by A.C.T.H., and regards this as only one indication of the effects of A.C.T.H. on body growth, eosinopenia, failure of granulation tissue formation, inhibition of chondro-osteogenesis and even diminution of lymphoid tissue. This effect on mitosis may prove important clinically and antagonistic to the newly discovered neoplasmodic action of growth hormone on viscera, including the lungs, to which Professor Herbert Evans briefly referred recently in a talk to the Endocrinological Society.

Physico-Chemical Isolation of Growth Hormone

In 1940 Fraenkel-Courat, Meamber, Simpson and Evans, reported the preparation of a cysteine

treated extract of pituitary growth hormone, which led to a purification and 'a marked decrease in the thyrotrophic, lactogenic and gonadotrophic hormone contamination.' In 1944 Li and Evans announced 'the isolation of pituitary growth hormone,' and in 1945 there was further information in a paper by Li, Evans and Simpson, entitled 'Isolation and properties of the anterior hypophyseal growth hormone.' The main features of the method of preparation were acetone dried powder, calcium hydroxide extract, globulin fractionation, sodium chloride fractionation, ammonium sulphate and isoelectric precipitation. From a solution of the hormone, ball-shaped 'particles' of uniform size and shape were precipitated and were found to have the same growth potency as the original solution. The hormone was protein in character, behaved as a single substance on electrophoresis, was free from lactogenic, thyrotrophic, adrenocorticotrophic or gonadotrophic activity, had a molecular weight of 44,250 and had an isoelectric point of pH 6.85. On 27-day hypophysectomized rats 0.010 mg. of the hormone caused an increase of 10 gm. in body weight when injected daily for ten days.

The Anatomy and Physiology of Bone Development

Bone is a highly specialized variety of connective tissue which is rendered rigid by the impregnation of its ground substance with calcium salts. The skeleton contains about 97 per cent. of the total calcium of the body. From the point of view of development there are two kinds of bones: (a) membranous (bones of the cranial vault) and (b) cartilaginous (long and most other bones). In both types embryonic connective tissue is transformed into bone by the activity of the specially modified fibroblasts known as osteoblasts; but whereas with membranous bone this is a direct process, with cartilaginous bone there is an intermediate deposition of cartilage which acts as a temporary framework and is ultimately replaced by true bone. In both instances the growth and changing shape of bones is a destructive as well as a constructive process. The former, which consists of the removal of the first-formed bone, is due to the activity of large multinucleated osteoclasts which originate from the same source as the osteoblasts and have the power of dissolving bone.

A long bone is at one stage a homogeneous cartilaginous structure. As such it can grow in any direction, except that it is invested with a thickening of embryonic connective tissue which tends to maintain its shape. This is the investing perichondrium and, at a later stage, the periosteum. At certain chronological stages, centres of ossification appear in the middle of

the shaft (diaphysis) and at either end (epiphyses) of the long bones. The process of ossification spreads from these centres outward, whilst from the periphery, or circumference, bone is laid down along the whole length of the shaft from the periosteal layer. Ultimately the whole of the bone and of the two ends become completely ossified, except for a line of cartilaginous cells which separates the shaft of the bone from either end. This important layer of cartilage (epiphyseal plate) is the site at which growth takes place. The cartilage cells proliferate, but the layer remains narrow as the proximal older cells are replaced by osteoid tissue which becomes calcified. Growth therefore takes place at both ends of a long bone. At a certain age, usually 16 to 18, the epiphyseal plate itself becomes replaced by bony tissue and the epiphysis is then said to be closed or to have joined the diaphysis. At this stage growth is no longer possible. In endocrine disorders, closure of the epiphyses may be premature or it may be delayed; even in apparently normal people there is a considerable variation in the age of closure.

Gleanings from Clinical Studies

The clinical facts of acromegaly and gigantism have been already dealt with in the first part of this article (April 1950), and are in harmony with our physiological knowledge. In 1946, Reifstein, Kinsell and Albright observed a high serum phosphorus in the active phase of acromegaly and in growing children, and that oestrogens by inhibiting the pituitary secretion of growth hormone in acromegaly, lowered the serum phosphorus. Li, Geschwind and Evans (1949) correlated this clinical finding with earlier knowledge of the lowering of serum phosphorus by hypophysectomy, and showed that pure growth hormone prevented this fall and even elevated the serum phosphorus level above that of the controls.

In clinical medicine, pituitary growth hormone as generally available has proved disappointing and usually futile, the only unequivocal exception in my experience being with very massive and painful doses in a girl of 18 with infantilism and open epiphyses, shown by me at the Endocrine Section of the Royal Society of Medicine on October 22, 1947 (not published). Dr. Hans Lissner in California informed me that in one case of infantilism where the pure crystalline growth hormone was made available, no growth and no nitrogen retention followed its use. The failure of growth may be related to the work of Freud, Levie and Kroon (1939), previously referred to, but the failure of nitrogen retention is more difficult to understand.

Testosterone (and occasionally oestrogens),

however, have a powerful augmenting influence on growth in infantilism and eunuchoidism, which is apparently contrary to the physiological experiments. From the point of view of the clinician, testosterone would have prior claim to the title of growth hormone, although experimentally it lacks any stimulating effects on epiphyseal cartilage growth. Kinsell, Michaels, Li and Larsen (1948) put forward the theory that there are two phases of growth (1) pre-pubertal, associated with high serum phosphorus and due to pituitary growth hormone, and (2) post-pubertal, associated with normal serum phosphorus and due to gonadal and adrenal androgens. They produce further evidence that androgens as well as oestrogens will depress serum phosphorus in acromegaly. Some eunuchs and eunuchoids may be tall and continue growing until the third decade of life; the epiphyses in these cases are open, and one must assume that growth is either due to continued secretion of pituitary growth hormone or to adrenal androgens. Growth is also accelerated with adrenal or gonadal sexual precocity and, since this includes female oestrogenic precocity, it would appear clinically that oestrogens as well as androgens can augment skeletal growth, although both also accelerate bone age and union of the epiphyses. In the syndromes of adipose gynandrisms and adipose gynism described in the Clinical Section of this article (April 1950) there is also augmented growth in childhood, but union of the epiphyses tends to be early in girls, e.g. 14, but not in boys, so that the ultimate height of the males tends to be on the tall side. There is no evidence, clinically or by assay, of an excess of adrenal androgens, so that the augmented growth must be ascribed to pituitary growth hormone and/or oestrogens. The occurrence of gynaecomastia in some of the males suggests oestrogens, as does the early closure of the epiphyses in the females. There is some evidence that diabetic children are taller than the average at the onset of their diabetes, and it is well known that inadequately controlled diabetic children do not grow as rapidly as normal children or well-controlled diabetics. These facts may be held to support the insulotrophic and diabetogenic action of growth hormone. The predisposition of fat people to diabetes in adult life may be correlated with a pituitary origin of the diabetes. A pituitary insulotrophic effect might be held to cause an initial adiposity, as there is experimental and clinical evidence for the conversion of carbohydrate to fat by insulin under certain conditions. This may also be the explanation of the adiposity in adipose gynandrisms and gynism, either as a direct pituitary stimulus or as a counteraction to adrenal 11-oxysteroids. However, the possibility of a more direct influence of adrenal steroids on

fat synthesis and deposition cannot be excluded.

These 'gleanings' from clinical studies are, it is appreciated, not entirely based on established foundations, but their hypothetical nature does not exclude their potential usefulness in the further exploration of growth and metabolism by the experimentalist and biochemist.

Conclusions

There is ample experimental evidence to indicate that the growth hormone is secreted by the eosinophil cells of the pituitary gland, and that the adrenals, thyroid, pancreatic islets and gonads produce hormones as a result of a pituitary stimulus. These bring about an important augmentation of growth hormone effect, and may even be effective in the absence of the pituitary gland. Nevertheless the pituitary growth hormone is a specific protein entity, now isolated from adrenotrophic, gonadotrophic, thyrotrophic, lactogenic and other hormones, which has a specific effect on epiphyseal cartilage, an activity associated with elevation of serum phosphorus. Such pure growth hormone has an insulotrophic and diabetogenic action under appropriate conditions, and the identity of these hormones has been postulated. From a therapeutic angle, testosterone has a powerful effect on somatic growth, not easily correlated with experimental evidence and different in character from that of growth hormone. In the author's clinical experience oestrogens may have a similar somatotrophic action in some types of infantilism and may succeed when androgens and growth hormone have failed.

Addendum

In the April number of this Journal the writer referred to a personal communication from Dr. R. G. Sprague of the Mayo Clinic, relating to the production of red and purple lineae disensae by cortisone injections. Attention was drawn to the importance of this as a basis for the diagnosis of hyperfunction of the adrenal cortex, not only in Cushing's classical syndrome, but in other conditions in which such coloured striae were present, and particularly in the syndrome described as adipose gynandrim and adipose gynism.

The actual article by Sprague and eight colleagues (1950) has since been received. Their first patient was a youth 17 years of age, who received 200 mg. of cortisone daily for 19 days, and 100 mg. daily for five additional days because

of acute rheumatic fever. Reddish purple striae were noted on the 24th day of treatment, when his weight had increased by 3 lb. They were over the hips and flanks. A second course of treatment with cortisone after an interval of 13 days, and lasting 28 days, led to the striae becoming broader and deeper in colour and a further increase in weight. Several weeks after stopping cortisone therapy, the striae lost their colour. Similar red or purple striae resulting from cortisone therapy were observed in six additional patients, five of whom were young.

Since the diabetogenic action of cortisone has been clearly demonstrated experimentally and in humans, particularly in Addison's disease, with or without co-existing diabetes mellitus, and since diabetogenic effects have been observed occasionally in Sprague's studies referred to above, it might be asked why diabetes was not present in the cases described by me as adipose gynandrim and gynism. The answer would appear to be that there is normally a balance between pancreatic insulin secretion on the one hand and pituitary and adrenal diabetogenic hormone on the other; and that when there is an excess of the latter hormones, or of cortisone itself, the islets of Langerhans respond by an excessive production of insulin to balance the diabetogenic tendency, which is thus hidden and undetected by blood sugar determinations. At a certain point the increased insulin secretion may become inadequate and hyperglycaemia then follows. It also seems probable that the secondary hyperinsulinism is an important factor in determining gain of weight and adiposity, although a more direct adrenal anabolic fat factor cannot be excluded. The insulintrophic action of pituitary growth hormone may also play a part.

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continued on page 435

incision. Special instruments and retractors made by Meyer and Phelps are helpful.

THORACIC APPROACH

An incision is made along the intercostal space between the 10th and 11th ribs. The thoracic cavity is opened, the ribs are retracted, and the diaphragm incised. The adrenal is held in special forceps and dissected from its bed. The diaphragm is repaired and the wound closed.

THE HIGH KIDNEY INCISION

An incision 6 to 8 in. long is made parallel to the last rib, and the muscles are divided. If the last rib is small it is resected sub-periostally and entrance gained into the perinephric fat by incision through its bed. If it is a large rib, two holes are made an inch apart at the neck, and the rib divided between them. A strong ligature is threaded through the holes and left *in situ* to be

tied when closing the wound. The perinephric fat is opened, the kidney held down with a special retractor, and a deep retractor pulls up the ribs. The adrenal gland is defined and caught in special forceps. Positive pressure is now applied by the anaesthetist and the gland dissected from its bed. The main vein seen on its inner border is then tied and the gland freed and removed. The vein is weak and if accidentally torn may give rise to alarming haemorrhage. This is more likely to happen if the diaphragm or vena cava are allowed to flap. The rib is then tied and the muscle layers are repaired with interrupted catgut. No drain is necessary and the skin is closed. Depending on the width of the subcostal angle, the plural or peritoneal cavity or both may be accidentally opened.

This operation has a shorter convalescence than the thoracic one, for in the latter, the lung may take some time to expand.

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